REMARKS

Upon entry of this amendment, Claims 1-37, 77, 83-94, 97-108 and 118-123 are now pending in the application, as originally or previously presented. Claims 1-37, 77, 84-87, 93, 94, 97 and 101-108 have been previously withdrawn. Claim 95 is cancelled herewith without prejudice, to expedite prosecution. Claims 38-76, 78-82, 96, 109-117 and 124-130 were previously cancelled. Claim 83 has been amended and The Examiner is respectfully requested to reconsider and withdraw the rejections in view of the amendments and remarks contained herein.

OBJECTION UNDER 35 U.S.C. § 1.75(C)

Claims 83 and 95 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. This objection has been rendered moot by the cancellation of Claim 95.

Accordingly, Applicants respectfully request that the present objection be reconsidered and withdrawn.

REJECTION UNDER 35 U.S.C. § 112

Claims 118 and 120 stand rejected under 35 U.S.C. § 112, first paragraph for allegedly lacking an enabling disclosure for the reasons of record as set forth in the Office Actions of 11/7/06, 7/19/07 and 4/10/08.

Applicants have provided ample extrinsic evidence to show that one of ordinary skill in the art would have been able to make and use the present invention without undue experimentation.

The present Office Action and previous Office Actions of 11/7/06, 7/19/07 and 4/10/08 generally allege a lack of enablement based on the contention that (1) the Applicants have not shown that the similar anti-idiotype response that was both therapeutic and prophylactic for its *in vivo* experiments in mice could be generated against a human xenograft of multiple myeloma or lymphoma cells in an animal model or could be used *in vivo* to treat against multiple myeloma or lymphoma, and (2) that the Applicants have not supported their assertion of enablement with extrinsic evidence that the general state of the art for nucleic acid vaccination is enabled.

Claim 118 is drawn to an isolated nucleic acid of claim 83, formulated for administration to a patient to induce production of the recombinant antibody-based dimeric molecule. Claim 120 is drawn to a cell line comprising a nucleic acid according to claim 83 or a vector containing the isolated nucleic acid of Claim 83.

Applicants respectfully submit that the bases for rejecting Claims 118 and 120 as noted in the present Office Action on pages 4-6 reiterating the comments of the Office Actions of 11/7/06, 7/19/07 and 4/10/08 are not relevant to the determination whether one of ordinary skill in the art would be guided by the specification and knowledge in the field to formulate the inventive nucleic acid and induce production of the recombinant vaccibody as recited in Claims 118 and 120. As previously stated in the response dated 7/10/08, the ability of the recombinant vaccibody of Claims 118 and 120 to generate therapeutic and prophylactic responses in any animal is irrelevant. The claims merely require that upon administration of the isolated nucleic acid of Claim 83 to a patient the isolated nucleic acid induces production of the recombinant antibody-based dimeric molecule *in vivo*.

With respect to the Action's second basis for lack of enablement, namely that the Applicants have not supported their assertion that the general state of the art along with the teachings provided in the Applicants' specification enables one of ordinary skill in the art to practice the claimed subject matter of claims 118 and 120. Applicants provide extrinsic evidence here with to support their argument that nucleic acid vaccination with the compositions of Claims 118 and 120 can be used to express the dimeric antibody DNA vaccine *in vivo*.

One of ordinary skill in the art could have referred to a number of sources of knowledge to supplement what is taught in the specification to practice the invention of Claims 118 and 120. For example, Kutzler, M. et al. (2008), describes the promising technology encompassed by DNA vaccine technology noting in particular: "In the past decade and a half, the DNA vaccine concept has been tested and applied against various pathogens and tumour antigens. In theory, this conceptually safe, non-live vaccine approach is a unique and technically simple means to induce immune responses." Kutzler, M et al, Nature Reviews Genetics(9): 776-788. (A copy is provided for the Examiner's convenience).

While applicants appreciate that this article was not available on or before the date of filing of the present application, several articles referenced in this review teaches that methods and successful implementation of such methods were known to those of ordinary skill in the art in DNA vaccine technology at the time of filing.

Tang, De-Chu et al. (1992) (abstract submitted herewith) referenced in the Kutzler review article discloses production of an immune reaction to a foreign protein by genetic immunization of the gene encoding the protein into the skin of mice. Hence the

observation that one can successfully effect expression of proteins from DNA constructs injected into mice dates at least back to 1992.

Wang et al. (1998) (abstract submitted herewith) discloses a DNA vaccination methodology against malaria. Human patients were immunized with a plasmid vector encoding a malaria protein. These patients developed antigen-specific CD8+ T-cell responses. More importantly, all 10 peptides tested resulted in immune responses that were restricted by six human lymphocyte antigen (HLA) class I alleles.

MacGregor, R.R. et al. (article submitted herewith) discloses human DNA vaccination using an effective HIV-1 construct that induced robust T-cell responses. "Our results demonstrate induction of a CD4 Th1 type response following DNA vaccination when HIV-1 expression vectors are administered as plasmid vaccines." MacGregor, at page 2141.

All of these methods and strategies for successful DNA vaccination belies the Action's contention that nucleic acid vaccination was not enabled by the examples and teachings of the Applicants' application and the knowledge of DNA vaccination by those of ordinary skill in the art at the time of filing the application. Thus, the extrinsic evidence presented by the Applicants is sufficient to support the Applicants' position that methods for nucleic acid vaccination using DNA vector constructs were known in the art and was enabled as of the date of filing the Applicants' specification. "The test for enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. ***A patent need not teach, and preferably omits, what is well***

known in the art." MPEP 2164.01 (citing *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991).

Applicants respectfully submit that the teachings provided by Applicants' specification for formulating a composition that can be used for DNA vaccination resulted in successful prophylactic and therapeutic responses in mice. The claims are further enabled when the teachings of the specification are coupled with the knowledge provided in the filed e.g. as described in the extrinsic evidence presented herein. Applicants respectfully submit that proper and sufficient evidence has been provided and that one of ordinary skill in the art could make and practice the claimed embodiments to the full scope of the inventive claims.

Accordingly, Applicants request that the present rejection of Claims 118 and 120 under 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn.

Claims 88-92 and 98 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point and distinctly claim the subject matter which Applicants regards as their invention. This rejection is respectfully traversed.

Claims 88-92 and 98 are alleged to be indefinite because it is unclear to the Office how the targeting unit is specific to APCs when, for example, chemokine receptors may be expressed on APCs and non-APCs alike. Further it is unclear to the Office how can the targeting unit be specific for only APCs when the targeting unit itself could potentially recognize other cells than APCs.

Claim 83 recites: "[w]herein each of said monomer unit comprises a targeting unit for an antigen presenting cell…" Applicants respectfully submits that Claim 83 does not

state that the targeting unit **is specific** for an antigen presenting cell. Additional claim limitations are being read into the ordinary meaning of the claims. While there are some ligands present on both APCs and non-APCs, Claim 83 and claims dependent thereon recite ligands that bind to APCs. One of ordinary skill in the art would readily recognize such a difference and would understand that Claim 83 and the ligands recited in Claims 88-92 and 98, i.e. soluble CD40 or a chemokine to be species of targeting units that are capable of binding to an APC. The metes and bounds of the claim scope would be readily discernable to one of ordinary skill in the art so as to avoid infringement. The role of the targeting ligand is that when an APC is present, the targeting ligand can bind to an APC that recognizes the targeting unit. The goal of the exemplified embodiments of the Applicants' DNA antibody vaccines is that high concentrations of vaccibodies are capable of binding to APCs through the affinity of the targeting ligand with the APC. This can be achieved if the targeting ligand is either APC specific or if the targeting unit is APC preferring, meaning that the targeting unit will bind preferably to APCs having numerous targeting ligand receptors (as opposed to targeting units that do not have the ability to target APCs over other immune cells) and therefore the goal of the vaccibody is met. In conclusion, Claims 88-92 and 98 as presently presented provide clarity of scope and would not be considered indefinite to one of ordinary skill in the art.

Accordingly, Applicants request that the present rejection of Claims 88-92 and 98 under 35 U.S.C. § 112, second paragraph be reconsidered and withdrawn.

REJECTION UNDER 35 U.S.C. § 102

Claims 83, 88-92, 95, 98-100, and 118-123 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Herman (U.S. Pub. No. 2005/0069549, published March 31, 2005, filed January 14, 2003). This rejection is respectfully traversed.

Applicant respectfully submits that Herman does not anticipate Claim 83 and claims dependent thereon because Herman fails to disclose each and every element as set forth in the amended claims either expressly or inherently described or its equivalent. MPEP § 2131

The amended Claim 83 recites "An isolated nucleic acid encoding a monomer unit of a recombinant antibody-based dimeric molecule, said nucleic acid encoding an antigenic unit, a dimerization motif and a targeting unit operably connected to encode said monomer unit, and wherein said antibody-based dimeric molecule comprises two of said monomer units connected through said dimerization motif, said dimerization motif comprising an Ig hinge region and a Cγ3 domain of each monomer unit, wherein each Ig hinge region contributes to dimerization via disulfide bridging to the other Ig hinge region and each Cγ3 domain contributes to dimerization via hydrophobic interactions to the other Cγ3 domain, and wherein each of said monomer unit comprises a targeting unit for an antigen presenting cell and an antigenic unit, **wherein said targeting unit and said antigenic unit in the monomer unit are separated by said dimerization motif** and wherein said monomer units each lack a CH2 domain."

Herman is drawn to multispecific ligands having at least one of the ligand binding moieties is a "targeting" arm in the sense that it at least preferentially recognizes a marker that is associated with one or more specific target entities eg. cell populations,

and the other ligand binding moiety is an "effector" arm which binds with relatively less affinity or functional affinity and/or less quickly to a target ligand which optionally has a more diverse biodistribution (Herman at page 3, par. [0024]). Herman is generally related to various antibody constructs or modification of antibodies, including for example "chimeric combinations of antibody regions or domains. (eg. FRs and CDRs) of different origins or species eg. humanized, any combination of one or more antibody fragments or recombinant reconstructions (scFvs) of antibodies including dimers, diabodies, triabodies, a myriad of known bispecific, trispecific, tetraspecific antibody formats or monovalent, divalent, trivalent, tetravalent or other multivalent antibody formats or any fragment, portion, or reconstruction of one or more portions of an antibody (scFv) or any truncated form a ligand binding entity, such antibody typically comprising at least a VH or VL portion or both or a functional portion of same (eg microbodies), including single domain antibodies, $F(ab')^2$, Fab, Fab', Facb, Fc, etc. (Herman at page 12, par. [0107]). With regards to the construction and alignment of possible antibody fragments, Herman teaches that the "[m]ultispecific ligand may comprise an Fc portion and a hinge portion and that one or both of a) the length, amino acid composition or* molecular weight (or various combinations of these interrelated factors) of the Fab or Fc portion; and b) the amino acid composition (including length) of the hinge portion (eg. any polypeptide segment that provides means for linking two typically heavy chains, eg. through one or more disulfide bonds, leucine zipper fos-jun, optionally a flexible hinge typical of an IgG1 or having one to several more disulfide bonds eg. IgG3)". (Herman at page 14, par. [0116]).

Herman discloses that the antibody components of the multispecific ligand can include one or both components (they may be the same or different) may be a dAb, a scFv, an Fab, a minibody moiety or a substantially intact antibody, for example both may be scFvs and the resulting product may be a diabody, triabody, or tetrabody. For example in a preferred embodiment the bispecific antibody comprises two dAb components comprising linked via a linker (see above) and having at least at least part of a constant region for fusion for example to a toxin (eg. at least a partial hinge region, and preferably also at least a partial CH2 domain optionally also at least a partial CH3 domain). (Herman at page 49, par. [0345]).

Applicants submit that Herman fails to teach or suggest a targeting unit and a antigenic unit in the monomer unit which are separated by a dimerization motif and wherein the monomer units each lack a CH2 domain. The constructs in Herman are devised to have an antibody units (a VH, VL $F(ab')^2$, Fab, Fab', Facb, Fc,) on the same side of a dimerization motif and hinge region. Applicants respectfully submit that all of the claim elements of the amended 83 must be found in Herman as arranged in the rejected claim. Picking various elements of the rejected claim from disparate constructs in Herman ence is not permitted. "The elements must be arranged as required by claim..." even if the identity of terminology is not required. MPEP 2131. In making the rejection of the claims under 35 U.S.C. § 102(e), Applicants respectfully request the Office to specifically point out and particularly cite to passages of Herman that discloses every claim limitation of the amended Claim 83 and Claims 88-92, 98-100 and 118-123. MPEP 2131.

Applicants respectfully submit, that for at least these reasons described above,

Herman fails to disclose each and every element of Claim 83, and thereby fails to anticipate Claim 83 and claims dependent directly or indirectly thereon.

Accordingly, Applicant respectfully requests that the present rejection under 35 U.S.C. § 102(e) of Claims 83, 88-92, 95, 98-100, and 118-123 be reconsidered and withdrawn.

CONCLUSION

It is believed that all of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the outstanding Office Action and the present application is in condition for allowance. Thus, prompt and favorable consideration of this amendment is respectfully requested. If the Examiner believes that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (248) 641-1600.

Respectfully submitted,

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